IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty Docket: Van den Brink-1

In re application of:	Art Unit: 1646
Gijs R. VAN DEN BRINK *et al.*	Examiner: Zachary C. HOWARD
Serial No. 10/505,230	
Filed: July 1, 2005	
For: HEDGEHOG-RELATED PROPHYLAXIS, THERAPY AND DIAGNOSIS OF GI TRACT CARCINOGENESIS	Confirmation No. 1902

DECLARATION UNDER 37 C.F.R. § 1.132 OF GIJS R. VAN DEN BRINK

Assistant Commissioner for Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Dear Sir:

I, the undersigned, declare as follows:

1. I am a co-inventor of the above-identified application. I received an M.D. and a Ph.D. degree from the University of Amsterdam in 1998 and 2002, respectively. I began working on in the field of gastroenterology on the basic biology of the gastrointestinal (GI) tract in 1998. My current emphasis is on the genetics and biology of GI cancer development and therapy. Currently, I am the Chief of the Laboratory of Gastroenterology & Hepatology at the Leiden University Medical Center in the Netherlands. I am an author of over 40 published papers and book chapters in my field. A copy of my *Curriculum Vitae* is attached to this Declaration as Appendix 2.

2. After the priority date and filing date of the above-identified patent application, I and my colleagues conducted experiments to test the ability of recombinant Hedgehog protein to prevent development of intestinal/colorectal cancer as discussed in the patent application. To this end, we transformed *Lactococcus lactis* (LL) bacteria (also referred to as "transgenic" bacteria) so that they secreted recombinant murine sonic hedgehog (mShh) protein, and upon introduction into a subject *in vivo*, did so in the murine distal small intestine and colon. This source of

Hedgehog protein was then tested for its ability to prevent cancer development. Several of the key experiments (not yet published) are reported below.

3. The LL bacteria were first shown to secrete the active 19 kDa N-terminal Shh polypeptide. See Figs. 1a and 1b of Appendix 1 to this Declaration.

4. The biological activity of the secreted mShh protein from the LL bacteria was demonstrated by the induction of alkaline phosphatase expression in C3H10T1/2 cells (Fig. 2). Culture supernatant of control (LL-EV) or mShh-secreting (LL-mShh) bacteria were examined in a standardized assay for Hedgehog protein activity (Katagiri *et al.*, 1990, *Biochem Biophys Res Commun 172*:295). Results show that the transgenic bacteria secreted significantly more biologically-active Shh than did the controls.

5. The effect of LL-mShh *in vivo* was examined in the small intestine of normal C57BL/6J mice after 7 days of once daily gastric inoculations with 250 μL of a suspension of bacteria that had grown to saturation density. Results are shown in Fig. 3. The concentration of total[1] Hedgehog protein in whole lysates of different segments of the small intestine were measured and are expressed as ng/ml measured by ELISA with monoclonal antibody 5E1[2] that is cross-reactive for all 3 murine Hedgehog proteins (Sonic, Indian, Desert). The results show that LL-mShh significantly increased the concentration of total hedgehog protein in the distal small intestine (as compared to the proximal duodenum), with the highest concentration in the ileum.

6. Finally, we delivered these bacteria to $APC^{+/min}$ mice by daily gavage, over a 4 week period, to test the ability of the Shh protein to prevent development of adenomatous polyps (murine model of FAP/sporadic colorectal carcinoma). These mice serve as an excellent model for GI tumor development of as they carry a heterozygous mutation in the *APC* gene which results in the formation of multiple adenomas, the precursors of adenocarcinomas, predominantly in the small intestine. This mutation affects the same gene as is affected in patients with familial adenomatous polyposis (FAP) and most sporadic colorectal carcinomas. The results are shown in Table 1 in Appendix 1. Administration of LL-mShh was found to prevent adenoma formation in the ileum (highly statistically significant), which is the site where most of recombinant mShh is secreted by the transformed bacteria (see ELISA results in Fig. 3).

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[1] endogenously expressed plus exogenous, LL-mShh-delivered

[2] Pepinsky RB *et al.*, , 2000, *J Biol Chem. 275*:10995-1001; Ericson, J *et al.*, 1995, *Cell* 81:747-56; Hunt R, *et al.*, 2007, *Hybridoma 26:*231-40.

7. The foregoing results confirm what was described in the patent application - already conceived by me and my co-inventors by the time the priority application was prepared. A "source of Hedgehog protein," in this case, in the form of transgenic *Lactococcus lactis* bacteria secreting Shh, had the following actions:

(a) The bacteria indeed secreted biologically active recombinant Shh protein;

(b) Secretion of this protein occurred *in vivo* in the small intestine, primarily in the distal small intestine (ileum); and,

(c) Most importantly, secretion of the recombinant Shh protein prevented the development of a form ("precursor") of GI cancer -- intestinal adenomas -- *in vivo*.

The application, together with these results, supports not only methods of treating cancer, but also supports methods for preventing G.I. cancer development.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to by true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: April 29, 2008 /s/ Gijs Robert van den Brink

Gijs Robert van den Brink

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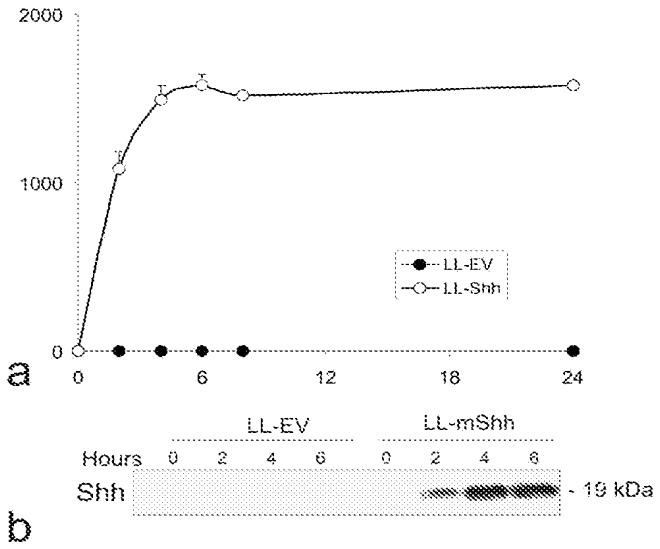
APPENDIX 1

FIGURES AND TABLE



Figs 1a and 1b. Fig.1a shows a time course (hrs) of concentrations (ng/ml) of murine Shh in supernatants of (i) control empty vector carrying LL (LL-EV) and (ii) Shh secreting LL (LL-Shh) as determined in a Hedgehog protein-specific ELISA using a monoclonal antibody 5E1 that recognizes all three hedgehog proteins. **Fig. 1b** shows a Western blot analysis of murine Shh 19 kDa polypeptide expression measured in supernatants of cultures of LL-EV and LL-mShh bacteria using the above antibody.

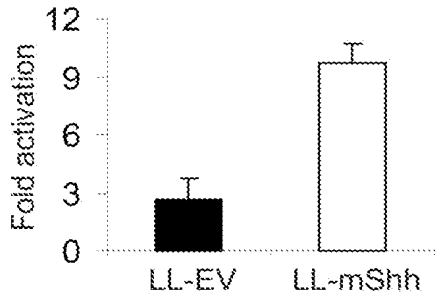


Fig. 2. mShh protein induces alkaline phosphatase expression in cells of the C3H10T1/2 line, measured as "fold-activation" of alkaline phosphatase (relative units). The effect of empty vectors (LL-EV) and Shh-secreting bacteria (LL-mShh) were compared. The assay used was a well-established assay of Hedgehog protein activity (Katagiri *et al. Biochem Biophys Res Commun* 1990;*172*:295).

APPENDIX 1

FIGURES AND TABLE

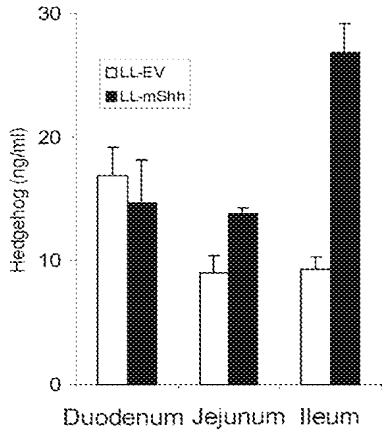


Fig. 3: Effect of LL-mShh *in vivo* in the small intestine of normal C57BL/6J mice after 7 days of once daily gastric inoculations with 250 μL of bacteria grown to saturation density (2×10^9 colony-forming units). Concentration of Hedgehog protein in whole lysates of different segments of the intestine (duodenum, jejunum, ileum) was measured by ELISA (using an antibody that recognizes all three hedgehog proteins).

Table 1

	Polyp number, 7 weeks	Polyp number, 11 weeks		New polyps during treatment	
		LL-EV	**LL-mShh**	**LL-EV**	**LL-mShh**
duodenum	1.0 ± 0.5	5.0 ± 1.0	5.7 ± 1.0	4.0 ± 1.0	4.7 ± 1.0
jejunum	7.8 ± 1.7	13.0 ± 3.4	9.8 ± 1.2	5.2 ± 3.2	2.0 ± 1.2
ileum	11.6 ± 2.4	24.6 ± 3.1	16.7 ± 1.8[a]	13.0 ± 2.9	5.1 ± 1.8[a]
colon	1.2 ± 0.5	1.2 ± 0.3	1.3 ± 0.3	0.0 ± 0.3	0.1 ± 0.3

[a] $P = 0.01$ by student *t*-test, LL-mShh (n = 12) compared to LL-EV (n = 11)

7 week old $APC^{+/min}$ mice were treated daily for four weeks by oral gavage with 250 μl of either LL-EV or LL-mShh grown to saturation density (see above). Polyps were enumerated as an estimate of the number of adenomas. Mice were sacrificed either at 7 weeks of age to determine the starting number of adenomas or after 4 weeks of daily treatment ("polyp number, 11 weeks") to evaluate the effect of the treatment. Reduction in adenoma formation (number of adenomatous polyps) was greatest in the ileum.

APPENDIX 2

Curriculum Vitae of Gijs Robert van den Brink

Home address:	17bis Chemin de Frenes, 1295 Tannay, Switzerland Tel: 0041-22-7768683
Work address:	Department of Gastroenterology & Hepatology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, Netherlands.
E- mail:	g.r.van_den_brink@lumc.nl
Born:	06-08-1970

Professional Experience, Training and Education

Jan 2008 -	**Chief, Laboratory of Gastroenterology & Hepatology** Department of Gastroenterology & Hepatology Leiden University Medical Center, Leiden, the Netherlands
Jan 2008 - July 2009	**Resident in Gastroenterology** Department of Gastroenterology & Hepatology Leiden University Medical Center, Leiden, the Netherlands
Jan 2006 - Jan 2008	Department of Gastroenterology & Hepatology Geneva University Hospital, Geneva, Switzerland
Sep 2006 - Jan 2008	**Postdoctoral Fellow** Laboratory of the Department of Gastroenterology & Hepatology Leiden University Medical Center, Leiden, the Netherlands
Jan 2003 – Jan 2008	**Postdoctoral Fellow** Department of Experimental Internal Medicine Academic Medical Center, Amsterdam, the Netherlands Department of Experimental Internal Medicine
Oct 2002-Oct 2005	**Resident in Internal Medicine** Academic Medical Center, Amsterdam, the Netherlands Department of Internal Medicine
Sep 1998-11 Dec 2002	**PhD, *cum laude*, University of Amsterdam** Thesis entitled: "Morphostasis of the adult gastrointestinal tract". Supervisors: Dr S.J. van Deventer and Dr M.P. Peppelenbosch
Oct 1989-24-02-98	**MD degree, University of Amsterdam** Academic Medical Center, Amsterdam, The Netherlands
1983 – 1989	**Murmellius Gymnasium**, Alkmaar, The Netherlands

Further Professional Experience

March 2001-May 2001	**Harvard University,** Boston, MA, USA Department of Pathology, Massachusetts General Hospital Studied gut morphogenesis (chick model) in lab of Dr DJ Roberts.
Jan 2001	**DNAX Research Institute,** Palo Alto, CA, USA Visiting scientist in the lab of Dr JD Sedgwick. Studied role of TNF in gastric hormone regulation
April 1998-Sep 1998	**Academic Medical Center, Amsterdam** Department of Pediatric Gastroenterology and Nutrition. Investigated determinants of the colonization pattern of *H. Pylori*.
Oct 1997- Dec 1997	**Academic Medical Center, Amsterdam** Department of Gastroenterology. Set up prospective randomized trial assessing the need to use conscious sedation in endosonography
Aug 1994– Aug 1995	**New England Medical Center, Tufts University,** Boston, MA, USA Departin ment of Pediatric Gastroenterology. Investigated regulation of intestinal genes in intestinal differentiation..
1994	**Academic Medical Center, Amsterdam** Department of Gastroenterology. Participated in trial of balloon dilatation of the sphincter of Oddi

Awards & Grants

Oct 2008	**ASNEMGE "Rising Star" Award** 'Rising star in Gastroenterology' award at the 2008 United European Gastroenterology Week in Vienna.
Dec 2007	**MLDS Grant** Awarded € 130.000 for project entitled: 'The role of Hedgehog signaling in colonic epithelial homeostasis'.
Aug 2007	**Yearly Ferring Fellowship** Awarded € 15.000/year to select one student per year to work in a lab specialized in IBD in the USA for a period of a year with a € 20.000 grant.
Jan 2007	**Organon Grant** Awarded € 283,791 for two year project that investigates the effect of sex hormones on colorectal cancer development.
Jan 2007	**Ferring Grant** Co-principle investigator on a € 93,930 two year project that will investigate the molecular mechanism of colitis associated colorectal carcinogenesis
Jan 2007	**UCB Grant** Co-principle investigator on a € 247,860 four year project that will investigate the mechanism of action of anti-TNF treatment in IBD
Dec 2005	**VENI Grant** Scored best project, NWO (Netherlands Organisation for Scientific Research) awarded € 200,000, for project entitled "Hedgehog signaling in colorectal carcinogenesis"
Dec 2005	**PhD Student Grant:** Awarded € 200,000 by the Academic Medical Center, Amsterdam
April 2003	**Emerging Leaders in Gastroenterology:** Invited member of a society that brings together young academic gastroenterologists from around the world.
Aug 2002	**PhD Student Grant:** Awarded € 200,000 by the Academic Medical Center, Amsterdam
2005	**Netherlands Society for Gastroenterology** Received "gastro start" € 7,000 grant that financed experiments that investigate the role of hedgehog signaling in colorectal carcinogenesis.
1994	**Glaxo Fellowship:** Awarded $ 20,000 for one year fellowship in a laboratory in the U.S.

Invited Lectures

Oct 2008	'Rising star in Gastroenterology' Lecture, UEGW Vienna, Austria, 2008
May 2008	'Rising star in Gastroenterology' Lecture, Digestive Disease Week, San Diego, CA, USA
Feb 2008	CNIO Cancer Conference, Centro Nacional de Investigaciones Oncológicas, Madrid, SPAIN
Jan 2008	Institut für Humangenetik, Göttingen University, Göttingen, GERMANY
Nov 2007	IBDnet Meeting, Barcalona, SPAIN
April 2007	Oasis Lecture, AMC, Amsterdam
Nov 2006	Journées de Gastroenterologie, Geneva, SWITZERLAND
Oct 2006	EMBO workshop on Hedgehog-Gli Signaling in Cancer and Stem Cells, Rome, ITALY
May 2006	Stowers Institute for Medical Research, Kansas City, MO, USA
Jun 2006	Lundberg Laboratory, Goteborg University, Goteborg, SWEDEN
Jan 2005	Invited speaker - Annual New Year's speech of Board of Directors of the AMC
July 2004	Breakfast Lecture, 10th Ann Meeting of Japanese Soc for Helicobacter Research, Tokyo
Jan 2004	Karolinska Institute, Stokholm, SWEDEN.
May 2003	"State of the Art" lecture at Current Topics in Gastroenterology, Faro, PORTUGAL.
May 2002	Clevers Laboratory, Utrecht, the NETHERLANDS.
May 2001	Department of Pathology Grand Rounds, Massachusetts General Hospital, Boston, USA.
Jan 2001	DNAX Research Institute, Palo Alto, CA, USA.
Nov 2000	Dept. of Cell Biology, Skirball Institute, NYU School of Medicine, New York, NY, USA.

LIST OF PUBLICATIONS

1. Bergman JJ, **Van den Brink GR**, Rauws EA, de Wit L, Obertop H, Huibregtse K, Tytgat GN, Gouma DJ. Treatment of bile duct lesions after laparoscopic cholecystectomy. **Gut**. 1996;38:141-7
2. **Van Den Brink GR**, Bloemers SM, Van Den Blink B, Tertoolen LG, Van Deventer SJ, Peppelenbosch MP. Study of calcium signaling in non-excitable cells. **Microsc Res Tech**. 1999;46:418-33
3. **Van Den Brink GR**, ten Kate FJ, Ponsioen CY, Rive MM, Tytgat GN, van Deventer SJ, Peppelenbosch MP. Expression and activation of NF-kappa B in the antrum of the human stomach. **J Immunol**. 2000;164:3353-9
4. **Van den Brink GR**, Tytgat KM, Van der Hulst RW, Van der Loos CM, Einerhand AW, Buller HA, Dekker J. H pylori colocalises with MUC5AC in the human stomach. **Gut**. 2000;46:601-7
5. Versteeg HH, Nijhuis E, **Van den Brink GR**, Evertzen M, Pynaert GN, van Deventer SJ, Coffer PJ, Peppelenbosch MP. A new phosphospecific cell-based ELISA for p42/p44 mitogen-activated protein kinase (MAPK), p38 MAPK, protein kinase B and cAMP-response-element-binding protein. **Biochem J**. 2000;350 Pt 3:717-22.
6. **Van den Brink GR**, O'Toole T, Hardwick JC, van den Boogaardt DE, Versteeg HH, van Deventer SJ, Peppelenbosch MP. Leptin signaling in human peripheral blood mononuclear cells, activation of p38 and p42/44 mitogen-activated protein (MAP) kinase and p70 S6 kinase. **Mol Cell Biol Res Commun**. 2000;4:144-50.
7. Hardwick JC, **Van den Brink GR**, Offerhaus GJ, van Deventer SJ, Peppelenbosch MP. NF-kappaB, p38 MAPK and JNK are highly expressed and active in the stroma of human colonic adenomatous polyps. **Oncogene**. 2001;20:819-27.
8. Hardwick JC, **Van Den Brink GR**, Offerhaus GJ, Van Deventer SJ, Peppelenbosch MP. Leptin is a growth factor for colonic epithelial cells. **Gastroenterology**. 2001;121:79-90.
9. **Van den Brink GR**, Hardwick JC, Tytgat GN, Brink MA, Ten Kate FJ, Van Deventer SJ, Peppelenbosch MP. Sonic hedgehog regulates gastric gland morphogenesis in man and mouse. **Gastroenterology**. 2001;121:317-28.
10. **Van Den Brink GR**, de Santa Barbara P, Roberts DJ. Epithelial cell differentiation-a Mather of choice. **Science**. 2001;294(5549):2115-6.
11. **Van den Brink GR**, van den Boogaardt DE, van Deventer SJ, Peppelenbosch MP. Feed a cold, starve a fever? **Clin Diagn Lab Immunol**. 2002;9:182-3.
12. **Van den Brink GR**, Hardwick JC, Nielsen C, Xu C, ten Kate FJ, Glickman J, van Deventer SJ, Roberts DJ, Peppelenbosch MP. Sonic hedgehog expression correlates with fundic gland differentiation in the adult gastrointestinal tract. **Gut**. 2002;51:628-33.
13. Van Den Blink B, Ten Hove T, **Van Den Brink GR**, Peppelenbosch MP, Van Deventer SJ. From extracellular to intracellular targets, inhibiting MAP kinases in treatment of Crohn's disease. **Ann N Y Acad Sci**. 2002;973:349-58.
14. de Santa Barbara P, **Van den Brink GR**, Roberts DJ. Molecular etiology of gut malformations and diseases. **Am J Med Genet**. 2002;115:221-30.
15. Bonta PI, Kok MF, Bergman JJ, **Van den Brink GR**, Lemkes JS, Tytgat GN, Fockens P. Conscious sedation for EUS of the esophagus and stomach: a double-blind, randomized, controlled trial comparing midazolam with placebo. **Gastrointest Endosc**. 2003;57:842-7.
16. Van den Brande JM, Braat H, **Van den Brink GR**, Versteeg HH, Bauer CA, Hoedemaeker I, van Montfrans C, Hommes DW, Peppelenbosch MP, van Deventer SJ. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. **Gastroenterology**. 2003;124:1774-85.
17. de Santa Barbara P, **Van den Brink GR**, Roberts DJ. Development and differentiation of the intestinal epithelium. **Cell Mol Life Sci**. 2003;60:1322-32.
18. Hardwick JC, **Van Den Brink GR**, Bleuming SA, Ballester I, Van Den Brande JM, Keller JJ, Offerhaus GJ, Van Deventer SJ, Peppelenbosch MP. Bone morphogenetic protein 2 is expressed by, and acts upon, mature epithelial cells in the colon. **Gastroenterology**. 2004;126:111-21.
19. **Van den Brink GR**, Bleuming SA, Hardwick JC, Schepman BL, Offerhaus GJ, Keller JJ, Nielsen C, Gaffield W, van Deventer SJ, Roberts DJ, Peppelenbosch MP. Indian Hedgehog is an antagonist of Wnt signaling in colonic epithelial cell differentiation. **Nat Genet**. 2004;36(3):277-82.
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21. Bleuming SA, Peppelenbosch MP, Roberts DJ, **Van den Brink GR**. Homeostasis of the adult colonic epithelium: a role for morphogens. **Scand J Gastroenterol**. 2004;39(2):93-8
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25. Suzuki H, Minegishi Y, Nomoto Y, Ota T, Masaoka T, **Van den Brink GR**, Hibi T. Down-regulation of a morphogen (sonic hedgehog) gradient in the gastric epithelium of Helicobacter pylori-infected Mongolian gerbils. **J Pathol**. 2005;206(2):186-97.
26. **Van Den Brink GR**, Peppelenbosch MP. Expression of hedgehog pathway components in the adult colon. **Gastroenterology**. 2006;130(2):619.
27. Bleuming SA, Kodach LL, Garcia Leon MJ, Richel DJ, Peppelenbosch MP, Reitsma PH, Hardwick JC, **Van den Brink GR**. Altered Bone Morphogenetic Protein signaling in the Helicobacter pylori infected stomach. **J Pathol**, 2006;209:190-7.
28. **Van den Brink GR**, Hardwick JC. Hedgehog Wnteraction in colorectal cancer. **Gut**, 2006;55:912-4.
29. Bos CL, Kodach LL, **Van den Brink GR**, Diks SH, Van Santen MM, Richel DJ, Peppelenbosch MP, Hardwick JCH. Effect of Aspirin on the Wnt/β-catenin pathway is mediated via Protein Phosphatase 2A. **Oncogene**, 2006;25:6447-56.
30. Xu CP, Ji WM, **van den Brink GR**, Peppelenbosch MP. Bone morphogenetic protein-2 is a negative regulator of hepatocyte proliferation downregulated in the regenerating liver.

    World J Gastroenterol. 2006;12:7621-5.
31. **Van den Brink GR, Offerhaus GJ**. The morphogenetic code and colon cancer development. **Cancer Cell**, 2007;11:109-117
32. Lowenberg M, Verhaar A, **Van den Brink GR**, Hommes DW. Glucocorticoid signaling: a nongenomic mechanism for T-cell immunosuppression. **Trends Mol Med**, 2007;13:158-63
33. Bleuming SA, He XC, Kodach LL, Hardwick JC, Koopman FA, Ten Kate FJ, Van Deventer SJ, Hommes DW, Peppelenbosch MP, Offerhaus GJ, Li L, **Van den Brink GR**. Bone Morphogenetic Protein signaling suppresses tumorigenesis at gastric epithelial transition zones in mice. **Cancer Res**, 2007;67:8149-55.
34. **Van den Brink GR**. Hedgehog signaling in development and homeostasis of the gastrointestinal tract. **Physiol Rev**, 2007;87:1343-75.
35. Kodach LL, Bleuming SA, Peppelenbosch MP, Hommes DW, **Van den Brink GR**, Hardwick JC. The effect of statins in colorectal cancer is mediated through the Bone Morphogenetic Protein pathway. **Gastroenterology**, 2007;133:1272-81.
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37. Kodach LL, Bleuming SA, Musler AR, Peppelenbosch MP, Hommes DW, **Van den Brink GR**, Van Noesel CJ, Offerhaus GJ, Hardwick JC. The Bone Morphogenetic Protein Pathway is active in human colon adenomas and inactivated in colorectal cancer. **Cancer**, 2008;112:300-6.
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39. Duijvestein M, **van den Brink GR**, Hommes DW. Stem cells as potential novel therapeutic strategy for inflammatory bowel disease. **J Crohn's Colitis**, 2008, in press.
40. Barros R, Pereira B, Duluc I, Azevedo M, Mendes N, Paulo P, Santos-Silva F, van Seuningen I, **van den Brink GR**, David L, Freund JN, Almeida R. Key elements of the BMP/SMAD pathway colocalize with Cdx-2 in intestinal metaplasia and regulate Cdx-2 expression in human gastric cell lines. **J Pathol**. In press.

Book Chapters

J Dekker, BJ van Klinken, KAMJ Tytgat, **GR van den Brink**, JHB van de Bovenkamp, M Verburg, IB Renes, HA Büller, AWC Einerhand. Regulation of mucin expression in the gastrointestinal tract. In: **Digestive mucus: from research to clinical implications**. J Bara, *et al.*, eds. Irvinn editions, Neuilly-sur-Seine 2000.

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